UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/079,834	05/15/98	MOUNTZ J	D6005

HM22/0619

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EXAMINER	
TUNG, M	
ART UNIT	**PAPER NUMBER**
1644	17

DATE MAILED: 06/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/079,834	Applicant(s) M untz And Zh u
	Examiner Mary B. Tung	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Apr 10, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 3-6, 8-16, 18, and 19* is/are pending in the applicat

Of the above, claim(s) *10-15* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, 8, 9, 16, 18, and 19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1, 3-6, 8-16, 18, and 19* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Upon reconsideration, the finality of the rejection of the Office action mailed 10/29/99, Paper No.10 is hereby withdrawn.

2. The amendment filed 12/3/99 has been entered as Paper No. 11

Claims 1-17 were originally presented.
Claims 10-15 stand withdrawn from consideration.
Claims 2 and 7 were cancelled in the paper filed 2/1/99, Paper No. 5
Claim 17 was cancelled in the paper filed 12/3/99, Paper No. 11.
Claims 18 and 19 were cancelled in Paper No. 11.
Claims 1, 3-6, 8, 9, 16, 18 and 19 are under consideration.

Specification

3. The specification is objected to because of the following informalities: on page 54, line 11, it appears that the sentence beginning with "There" should be "These". Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 102

4. In light of the cancellation of Claim 17 in the paper filed 12/3/99, Paper No. 11, the rejection under 35 U.S.C. 102(e) as being anticipated by Bellgrau (US Patent #5,759,536), is hereby withdrawn.

Claim Rejections - 35 U.S.C. § 103

5. Claims 1 and 3-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Süss *(J. Exp. Med. 183:1789-1796, 1996)*.

6. Bellgrau, et al. (US Patent No. 5,759,536) teaches a method of inhibiting T-lymphocyte-mediated immune responses by providing a recipient animal with Fas ligand or cells expressing Fas ligand. The '536 patent additionally teaches the use of said method to improve organ transplantation and to treat juvenile diabetes (see the abstract, col. 3, lines 42-55, col. 6, lines 64-68 and claims 1-3 and 7, in particular). However, the '536 patent does not teach the use of antigen presenting cells to express Fas ligand in said method. However, Süss teaches that $CD8^+$ dendritic cells express Fas ligand and induces apoptosis of $CD4^+$ T cells which results in the down regulation of the immune response. Süss also teaches that the expression of Fas ligand by cell of the anterior chamber of the eye and Sertoli cells provide for the killing of Fas expressing T cells and thus makes these tissues immune-privileged sites. Süss

additionally teaches that the same mechanism probably occurs with dendritic cells and that whole animal models are needed to assess the relative importance of different Fas-ligand expressing cells in controlling immune responses (see the abstract, page 1792, col. 2, paragraph 3, page 1793, and page 1795, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Süss in the method of immunosuppression taught by the '536 patent in order to improve transplantation success or for the treatment of an autoimmune disease such as diabetes, as taught by the '536 patent (see the abstract and col. 3, lines 51-55, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. The Examiner again maintains that the article by Chen and Wilson, provided by the Applicants with Paper Nos. 5, 6, and 11 is not persuasive, because even though the authors discussed the "ingenuity" of the invention, does not provide evidence that the cited teachings of Süss and Schuler do not encompass the claimed invention. The Applicants argue the article by Chen post-dates both the Süss and Schuler references and reason that "if the teachings of Süss and Schuler rendered the present inventions obvious, the inventions would not have been considered "ingenious" by Chen and Wilson." However, the reference by Chen and Wilson do not clearly point out the *patentable* novelty which the Applicants think the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections. They are opinions not based in the legal definition of 35 U.S.C. 103(a). Additionally, Chen and Wilson teach that the Applicants' invention would require the generation of Fas-deficient antigen presenting cells from every patient for the method to work in humans (see page 1012, col. 3), and therefore, the reference by Chen and Wilson would be outside the scope of the instant disclosure, since the Applicants used Fas deficient mice or used in vitro experiments wherein apoptosis was measured ex vivo (see Examples 5 and 8-10, and so forth). As Applicants stated on page 11 of Paper No. 16, that "It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results." The Applicants additionally argue in Paper No. 11 that Kang, et al. "report that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection." The Applicants also argue that Chen, Sun and Nabel (no citation provided - first provided with the Appellants' Brief, filed 4/10/2000, Paper No. 16) report subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophil activation and rejection of the cancer cells and "Hence, expression of Fas ligand does not always inhibit immune responses." The Applicants also indicate that the regulatory function of Fas ligand is more complex and

varies between different experimental and in vivo settings." However, one of skill in the art would have an expectation of success given the teachings by Süss, et al., Schuler, et al., and the '536 patent which teach the suppression of the immune response using the Fas/Fas ligand system. The limitation added to Claim 1 in Paper No 11, is a recited mechanism, which adds no patentable weight to the claim. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 1 and 3-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Schuler, et al. *(Int. Arch. Allergy Immunol. 112:317-322, 1997)*.

9. Bellgrau has been discussed, *supra*. However, the '536 patent does not teach the use of antigen presenting cells to express Fas ligand in said method. However, Schuler teaches that dendritic cells express Fas ligand and may provide a novel approach to induce tolerance in transplantation and autoimmunity (see the abstract, page 320, col. 2, paragraph 2, and page 321, col. 2, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Schuler in the method of immunosuppression taught by the '536 patent in order to induce tolerance for the treatment of transplantation or autoimmune disease such as diabetes, as taught by Schuler. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. The Applicants argue that Schuler, et al. is a review article which does not demonstrate a method of inducing antigen-specific systemic tolerance by administering antigen presenting cells expressing Fas ligand and the antigen. The Applicants repeated their arguments concerning the '536 patent, discussed, *supra*. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, Schuler teaches that dendritic cells express Fas ligand and may provide a novel approach to induce tolerance in transplantation and autoimmunity (see the abstract, page 320, col. 2, paragraph 2, and page 321, col. 2, in particular). Dendritic cells are well known in the art to be antigen presenting cells. Therefore, one of ordinary skill in the art at the time

the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Schuler in the method of immunosuppression taught by the '536 patent in order to induce tolerance for the treatment of transplantation or autoimmune disease such as diabetes, as taught by Schuler. The Applicants argue that Chen and Wilson and Kang, et al. teach away from the claimed invention by teaching that inflammation and immune cell infiltration can result in the expression of Fas ligand. The Applicants additionally argue in Paper No. 11 that Kang, et al. "report that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection." The Applicants also argue that Chen, Sun and Nabel (no citation provided - first provided with the Appellants' Brief, filed 4/10/2000, Paper No. 16) report subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophil activation and rejection of the cancer cells and "Hence, expression of Fas ligand does not always inhibit immune responses." The Applicants also indicate that the regulatory function of Fas ligand is more complex and varies between different experimental and in vivo settings." However, one of ordinary skill in the art would have an expectation of success given the teachings by Süss, et al., Schuler, et al., and the '536 patent which teach the suppression of the immune response using the Fas/Fas ligand system. The limitation added to Claim 1 in Paper No 11, is a recited mechanism, which adds no patentable weight to the claim. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claim 16 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Süss, et al. *(J. Exp. Med. 183:1789-1796, 1996)*.

12. Bellgrau, et al. (US Patent No. 5,759,536) teaches a method of inhibiting T-lymphocyte-mediated immune responses by providing a recipient animal with Fas ligand or cells expressing Fas ligand. The '536 patent additionally teaches the use of said method to improve organ transplantation and to treat juvenile diabetes (see the abstract, col. 3, lines 42-55, col. 6, lines 64-68 and claims 1-3 and 7, in particular). However, the '536 patent does not teach the use of antigen presenting cells to express Fas ligand in said method. However, Süss teaches that $CD8^+$ dendritic cells express Fas ligand and induces apoptosis of $CD4^+$ T cells which results in the down regulation of the immune response. Süss also teaches that the expression of Fas ligand by cell of the anterior chamber of the eye and Sertoli cells provide for the killing of Fas expressing T cells and thus makes these tissues immune-privileged sites. Süss additionally teaches that the same mechanism probably occurs with dendritic cells and that whole animal models are needed to assess the relative importance of different Fas-ligand expressing cells in controlling immune responses (see the abstract, page 1792,

col. 2, paragraph 3, page 1793, and page 1795, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Süss in the method of immunosuppression taught by the '536 patent in order to improve transplantation success or for the treatment of an autoimmune disease such as diabetes, as taught by the '536 patent (see the abstract and col. 3, lines 51-55, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. The Applicants repeated their arguments concerning the '536 patent and Süss, et al. The Applicants argue that "The combined references to not have any data on the effect of Fas ligand expression on antigen presenting cells in vivo. In the absence of the necessary teaching or suggestion that Fas ligand expression in the in vivo situations described in Applicant's claimed invention would have inhibitory rather than stimulatory effects, the combined teaching will not lead one of ordinary skill in the art to the claimed invention." Further, the Applicants argue that the references do no teach the novel adenovirus system are not taught or suggested in the combined references. However, one of ordinary skill in the art would have an expectation of success given the teachings by Süss, et al., Schuler, et al., and the '536 patent which teach the suppression of the immune response using the Fas/Fas ligand system. The Examiner also notes that the Applicants used Fas deficient mice or used *in vitro* experiments wherein apoptosis was measured *ex vivo* (see Examples 5 and 8-10, and so forth). As Applicants stated on page 11 of Paper No. 16, that "It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results." Additionally, in response to Applicants's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicants relies (i.e., the use of the novel adenovirus vector system) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Süss in the method of immunosuppression taught by the '536 patent in order to improve transplantation success or for the treatment of an autoimmune disease such as diabetes, as taught by the '536 patent (see the abstract and col. 3, lines 51-55, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the

time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 16 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Bellgrau (US Patent No. 5,759,536) in view of Schuler, et al. *(Int. Arch. Allergy Immunol. 112:317-322, 1997)*.

15. Bellgrau has been discussed, *supra*. However, the '536 patent does not teach the use of antigen presenting cells to express Fas ligand in said method. However, Schuler teaches that dendritic cells express Fas ligand and may provide a novel approach to induce tolerance in transplantation and autoimmunity (see the abstract, page 320, col. 2, paragraph 2, and page 321, col. 2, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Schuler in the method of immunosuppression taught by the '536 patent in order to induce tolerance for the treatment of transplantation or autoimmune disease such as diabetes, as taught by Schuler. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. The Applicants repeated their arguments concerning the '536 patent and Schuler, et al. The Applicants argue that "The combined references to not have any data on the effect of Fas ligand expression on antigen presenting cells in vivo. In the absence of the necessary teaching or suggestion that Fas ligand expression in the in vivo situations described in Applicant's claimed invention would have inhibitory rather than stimulatory effects, the combined teaching will not lead one of ordinary skill in the art to the claimed invention." Further, the Applicants argue that the references do no teach the novel adenovirus system are not taught or suggested in the combined references. However, one of ordinary skill in the art would have an expectation of success given the teachings by Süss, et al., Schuler, et al., and the '536 patent which teach the suppression of the immune response using the Fas/Fas ligand system. The Examiner also notes that the Applicants used Fas deficient mice or used *in vitro* experiments wherein apoptosis was measured *ex vivo* (see Examples 5 and 8-10, and so forth). As Applicants stated on page 11 of Paper No. 16, that "It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results." Additionally, in response to Applicantt's argument that the references fail to show certain features ofApplicant's invention, it is noted that the features upon whichApplicant relies (i.e., the use of the novel adenovirus vector system) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re*

Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use Fas-ligand-expressing dendritic cells, taught by Schuler in the method of immunosuppression taught by the '536 patent in order to induce tolerance for the treatment of transplantation or autoimmune disease such as diabetes, as taught by Schuler. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following are new grounds for rejection:

Claim Rejections - 35 U.S.C. § 112

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1, 3-6, 8, 9, 16 and 18 are rejected under *35 U.S.C. 112*, first paragraph, because the specification, while being enabling for a method of inducing systemic immune tolerance in C57BL6-*lpr/lpr* mice by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells, does not reasonably provide enablement for a method of inducing systemic immune tolerance in an individual, by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells, in general, particularly in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

19. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the method inducing systemic immune tolerance in C57BL6-*lpr/lpr* mice by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells, the specification fails to provide guidance as to a method of inducing systemic immune tolerance in any individual, in

general using by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells. This claim would encompass the use of said vector in humans. The Applicants disclose that the C57BL6-*lpr/lpr* mice are deficient in the expression of *Fas,* (see page 36, line 21 and bridging over to page 37, line 4), the Applicants have not provided guidance as to how the claimed invention would work in individuals, either mouse or primate, that naturally expressed *Fas*. Therefore, the Applicants have not disclosed how one of skill in the art would be able to use an adenoviral vector in species other than mice. Houghton, et al. *(Clin. Cancer Res. 3:2205-2209, 1997)* teach that *Fas* is constitutively expressed in humans in the thymus, lung, spleen; in a variety of epithelial tissues, including the small and large intestines; and also the seminal vesicle, prostate and uterus (see page 2205). Itoh, et al. *(Cell, 66:233-243, 1991)* teaches that *Fas* is expressed on human myeloid cells, T lymphoblastoid cells and fibroblasts (see page 233, col. 2). With the wide variety of human cells which express *Fas*, the Applicants have provided insufficient guidance how to one of skill in the art would use the method disclosed in mice deficient in the expression of *Fas* to the claimed method in other individuals which express constitutively express *Fas*. The Applicants additionally argue in Paper No. 11 that Kang, et al. "report that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection." The Applicants also state in Paper No. 11 that Chen, Sun and Nabel. report subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophil activation and rejection of the cancer cells. Hence, expression of Fas ligand does not always inhibit immune responses." The Applicants also indicate that the regulatory function of Fas ligand is more complex and varies between different experimental and in vivo settings." Additionally, Chen and Wilson teach that the Applicants' invention would require the generation of Fas-deficient antigen presenting cells from every patient for the method to work in humans (see page 1012, col. 3), and therefore, the reference by Chen and Wilson would be outside the scope of the instant disclosure, since the Applicants used Fas deficient mice or used *in vitro* experiments wherein apoptosis was measured *ex vivo* (see Examples 5 and 8-10, and so forth). As Applicants stated on page 11 of Paper No. 16, that "It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results." In view of this statement from the Applicants, although a method of inducing systemic immune tolerance in Fas-deficient C57BL6-*lpr/lpr* mice by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells, there is no evidence of record to show that one skilled in the art would associate the said *in vivo* mouse method with the successful method of inducing systemic immune tolerance in any individual in general, by administering antigen presenting cells expressing Fas ligand to an individual, wherein said antigen presenting cells induce apoptosis of Fas-positive cells, as claimed herein.

20. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

21. Claim 19 is rejected under *35 U.S.C. 112*, first paragraph, because the specification, while being enabling for a method of inducing systemic immune tolerance in C57BL6-*lpr/lpr* mice using an adenoviral vector, does not reasonably provide enablement for a method of inducing systemic immune tolerance in an individual, using an adenoviral vector, in general, particularly in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

22. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the method inducing systemic immune tolerance in C57BL6-*lpr/lpr* mice using an adenoviral vector (see pages 10-11 and Example 3, in particular), the specification fails to provide guidance as to a method of inducing systemic immune tolerance in any individual, in general using an adenoviral vector. This claim would encompass the use of said vector in humans. Anderson *(Nature 392(suppl):25-30, April 1998)* teaches that "[adenoviral trials] results in animals have not always reflected what happens in [human] patients" (bracketed term added by Examiner for clarity). Additionally, in response to the University of Pennsylvania adenoviral clinical study, wherein a study subject died, Fox *(Nature Biotechnology 18:143-144, Feb. 2000)*, teaches that the safety characteristics of the adenoviral vector used by the U. Penn researchers (headed by James Wilson) were good, based on studies in mice. Fox also teaches that Wilson indicated that "the doses at which there are toxic effects or potential therapeutic effects may be separated only narrowly, and there may be thresholds where adverse effects abruptly appear - complicating how vectors might be used and perhaps undermining the reliability of results from tests in animals." Also, "Equally, if not more problematic for would-be gene-therapy procedures, these vectors are not so reliable in delivering genes where they are targeted." The adenovirus in the trial subject had "spread widely through other organs and also, at least early on, into immune system cells, based on the post mortem analysis of his tissues - distributing quite differently from how it behaved during animal experiments, according to Wilson." (see page 144). Furthermore, Marshall *(Science 288:951-957, May 2000)* teaches that "Relying on mouse studies, they [the Wilson team] had expected to see adenovirus concentrated in the liver. Instead, as a most mortem revealed, the vector was everywhere. To figure out what

happened, Wilson gave the vector intravenously to mice. Tagged adenovirus vector first appeared in macrophage or scavenger cells in the liver.... Later it reached the intended target, primary liver cells (hepatocytes)." "Animal data may have given clinicians false hope that adenovirus would work well in the human liver..... In fact, "rodents models might be misleading" for gene therapy, says Jeffrey Bergelson of the Children's Hospital of Philadelphia" (see pages 954 and 955).

23. Additionally, the C57BL6-*lpr/lpr* mice are deficient in the expression of *Fas,* (see page 36, line 21 and bridging over to page 37, line 4), the Applicants have not provided guidance as to how the claimed invention would work in individuals, either mouse or primate, that naturally expressed *Fas*. Therefore, the Applicants have not disclosed how one of skill in the art would be able to use an adenoviral vector in species other than mice. Houghton, et al. *(Clin. Cancer Res. 3:2205-2209, 1997)* teach that *Fas* is constitutively expressed in humans in the thymus, lung, spleen; in a variety of epithelial tissues, including the small and large intestines; and also the seminal vesicle, prostate and uterus (see page 2205). Itoh, et al. *(Cell, 66:233-243, 1991)* teaches that *Fas* is expressed on human myeloid cells, T lymphoblastoid cells and fibroblasts (see page 233, col. 2). With the wide variety of human cells which express *Fas*, the Applicants have provided insufficient guidance how to one of skill in the art would use the method disclosed in mice deficient in the expression of *Fas* to the claimed method in other individuals which express constitutively express *Fas*. The Applicants additionally argue in Paper No. 11 that Kang, et al. "report that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection." The Applicants also state in Paper No. 11 that Chen, et al. report subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophil activation and rejection of the cancer cells. .. Hence, expression of Fas ligand does not always inhibit immune responses." The Applicants also indicate that the regulatory function of Fas ligand is more complex and varies between different experimental and in vivo settings." Additionally, Chen and Wilson teach that the Applicants' invention would require the generation of Fas-deficient ANTIGEN PRESENTING CELLS from every patient for the method to work in humans (see page 1012, col. 3), and therefore, the reference by Chen and Wilson would be outside the scope of the instant disclosure, since the Applicants used Fas deficient mice or used in vitro experiments wherein apoptosis was measured ex vivo (see Examples 5 and 8-10, and so forth). As Applicants stated on page 11 of Paper No. 16, that "It is well known to a person having ordinary skill in this art that one cannot always equate in vitro to in vivo results." In view of this statement from the Applicants, although a method of inducing systemic immune tolerance in C57BL6-*lpr/lpr* mice using an adenoviral vector are disclosed in the specification, there is no evidence of record to show that one skilled in the art would associate the said *in vivo* mouse method with the successful method of inducing systemic immune tolerance in any individual in general, using an adenoviral vector, as claimed herein.

24. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Conclusion

25. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

26. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Tuesday through Friday from 8:30 am to 6 pm, and on alternating Mondays. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

June 16, 2000
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

DAVID SAUNDERS
PRIMARY EXAMINER
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